Johnson & Johnson

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Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 2006N-0061 – Charging for Investigational Drugs

These comments are submitted on behalf of the Johnson & Johnson Family of Companies (J&J) in response to the proposed rules on charging for investigational drugs that were published in the Federal Register on December 14, 2006. J&J sponsors or supports many clinical trials and has a strong interest in the rules that govern trials.

J&J is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets. J&J has more than 200 operating companies in 54 countries around the world employing approximately 110,600 employees and selling products in more than 175 countries. The fundamental objective of Johnson & Johnson is to provide scientifically sound, high quality products and services to help heal, cure disease, and improve the quality of life.

J&J's principal comments on the proposal, which are discussed in detail below and largely relate to charging for approved drugs, can be briefly summarized as follows:

- Sponsors and investigators should be permitted to charge for approved drugs used for their FDA-approved and other medically accepted (i.e., compendium-listed) uses without any additional showing.
- If the rules include specific provisions on charging for approved drugs used as active controls or in combination with investigational drugs, there should not be a distinction between the sponsor's own drugs and the drugs of other manufacturers.
- When an investigational drug is studied in combination with standard-therapy drugs, charging should ordinarily be permitted for the standard-therapy drugs.
- If Medicare covers a drug used in a clinical trial under its coverage with evidence development policy, FDA should permit charging for the drug.

- When charging is permitted for approved drugs, normal charges and insurance reimbursement should be allowed, rather than limiting charges to cost-pass-through amounts as proposed.
- FDA should reconsider the reduced charge proposed to be allowed for unapproved drugs, especially drugs furnished in an expanded access program, because the low charge may be inconsistent with fostering patient access to the drugs.
- Prior FDA approval should not be required to charge for approved drugs that meet the criteria for charging.
- The regulations should explicitly provide that IND-exempt trials are not subject to the restrictions on charging.

Criteria for Permissible Charging

The Proposed Rule:

In the case of a company-sponsored trial, the proposal would generally prohibit the sponsor from charging for its own investigational drugs or its own approved drugs being studied for a new use. Charging for a drug would be permitted only if (a) the drug could provide a significant advantage over available products, (b) the clinical trial is essential to FDA approval of the drug or its new use, and (c) the trial could not be conducted without charging because the cost of the drug is "extraordinary." Charging would be permitted in expanded access programs only if the charging would not interfere with the sponsor's program of registrational trials.

More lenient criteria would apply if the trial sponsor must acquire drugs from another entity. These criteria would apply if (a) a company-sponsor wanted to charge for the approved drugs of other manufacturers used in a trial as active controls or in combination with the sponsor's drug, or (b) a sponsor wanted to study a drug that had to be obtained from another entity. In those circumstances, charging would be permitted if the study is adequately designed and the other company's drug is not available for free.

Comments:

- **Charging for Approved Drugs – In General**

The proposed regulation specifically identifies categories of approved drugs for which the sponsor may charge under certain conditions: (a) the sponsor's own drugs if they are being studied for a new use, and (b) drugs that the sponsor must obtain from another entity if the drugs are being studied in the trial or are being used as a comparator to, or in combination with, the studied drug. The proposal does not, however, address the complete range of uses for which approved drugs may be furnished in clinical trials. For example, in the trial of an investigational anticancer drug, patients may receive antiemetics, hematopoietic growth factors, and other approved supportive care drugs administered in accordance with their FDA-approved labeling or other medically accepted practice. We recommend that the proposal on charging for approved drugs should be revised and clarified in several important respects.

Initially, we believe that the FDA rules should explicitly distinguish between charging for approved drugs that are being investigated for a new use and charging for approved drugs that are being used in accordance with their FDA-approved or other medically accepted uses (by which we mean uses supported by one of the recognized compendia).[1] The proposal does not clearly make that distinction.

Under one reading of both the current and proposed regulations, approved drugs that are used for non-investigational purposes might nevertheless be viewed as investigational drugs and therefore subject to the charging restrictions. Although we do not think that result was intended, the regulations define an investigational drug as any drug used in a clinical investigation, and they define a clinical investigation as any use of a drug other than the use of a marketed drug in the course of medical practice.[2] These potentially sweeping and confusing provisions defining the drugs that are subject to the charging restrictions should be clarified. The regulations should explicitly provide that there are no restrictions on charging for approved drugs furnished to patients in a clinical trial if the drugs are not a subject of the investigation, which we believe is the intent of both the current regulations and the proposed changes.

Such a policy would be consistent with current practice. Medicare, for example, pays for supportive care drugs and other non-investigational drugs used in clinical trials as, typically, do other health insurers.[3] FDA policy on charging should not be more restrictive than the policies of governmental and other third-party payers regarding reimbursement for drugs used in clinical trials.

Moreover, the reasons advanced in the proposal to prohibit charging for drugs used in trials appear to have been developed with investigational uses in mind and do not readily apply to drugs being used for medically accepted purposes.

The preamble states that trial subjects should not be charged for exposing themselves to the risks of an unproven drug, but that rationale does not apply to an approved drug used for a medically accepted purpose. It also states that clinical trial expenses are a cost of doing business that can be recouped by eventually marketing the approved drug for its approved indication. The costs of providing medically accepted therapies to patients should not be transferred ultimately to the purchasers of a future drug simply because the patients happen to receive the medically accepted therapies in a clinical trial. Those patients receive standard care that is recognized as care for which the costs are appropriately allocated to patients and health insurance plans, including Medicare. The proposal implicitly recognizes that not all drug costs should be considered a cost

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[1] As is well-known, many drugs are used for "off-label" purposes that, while not included in the FDA-approved labeling of the product, are supported by the scientific literature and may well be the standard of care. Such uses are typically listed in compendia such as the *United States Pharmacopeia – Drug Information* or the *American Hospital Formulary Service*. Federal law requires the Medicare and Medicaid programs to reimburse for such uses, 42 U.S.C. §§ 1395w-102(e)(1), 1395x(t)(2)(B), 1396r-8(k)(6), as do many state laws regulating health insurance. Medically accepted off-label uses should be treated the same as FDA-approved uses for the purposes of determining when charging for drugs is permitted.

[2] 21 C.F.R. § 312.3(b).

[3] See, e.g., Medicare National Coverage Determinations Manual § 310.

of conducting trials by allowing sponsors to charge for the approved drugs of other manufacturers that are used as active controls or in combination with an investigational drug.

In the following paragraphs, we address some specific situations involving approved drugs. More generally, we recommend that FDA make explicit a broad policy that trial sponsors may charge for approved drugs used in accordance with their FDA-approved labeling or otherwise in accordance with medically accepted uses. No additional criteria should have to be satisfied in such cases.

- **The Sponsor's Own Approved Drugs Used As Active Controls or In Combinations**

There appears to be a gap in the proposed regulations with respect to approved drugs used as active controls and in combinations. The proposal addresses the sponsor's own approved drugs being investigated for a new use, and it addresses approved drugs obtained from other manufacturers for use as active controls or in combination with an investigational drug. The proposal does not, however, explicitly deal with trials in which a company-sponsor is using its own approved drugs as the active control or the approved components of a combination.

Active controls are often used when a placebo control would be unethical, such as in studies of cancer drugs. For similar reasons, the test arm of a study might consist of the active control in combination with the study drug, rather than the study drug alone, so that seriously ill patients in the test arm are not denied the benefits of the proven therapy.

If a company-sponsor can charge for active control and combination-component drugs obtained from another manufacturer, as the proposal would allow, there is no reasonable basis to treat the sponsor's own drugs differently. As outlined above, we believe that charging for approved drugs used for medically accepted purposes should be explicitly allowed in general, but if FDA policy specifically allows charging for approved drugs used as active controls and in combinations, that policy should apply to the sponsor's own drugs as well as to drugs obtained from other companies. The cost of approved drugs used in a trial for medically accepted purposes is not a drug development expense that should be borne by the sponsor, regardless of what company manufactured the drugs.

- **Approved Drugs Used in Combination with Investigational Drugs**

Under the proposal, an approved drug that is used in accordance with its FDA-approved labeling or medically accepted practice would be subject to the charging restrictions if it is used in combination with the drug being investigated. We believe that this proposed policy is overly broad and should be narrowed.

As indicated above, certain types of drugs, such as cancer drugs, are frequently studied by comparing the current standard-of-care drug regimen to a combination of the standard-of-care regimen and the new drug. The drugs in the standard-of-care regimen will often be manufactured by companies other than the sponsor of the new drug.

If a patient is receiving approved drugs that are being used in a medically accepted manner in combination with an investigational drug, the medically accepted drug uses should generally not be the subject of charging restrictions. Ordinarily, the new drug will be additive to the

effectiveness of the medically accepted regimen, and the patient will receive the full benefit of the current regimen. In such a case, the approved drugs should not be regarded as investigational and subject to charging restrictions. The final rule should set forth criteria to identify the unusual cases when trial subjects would not receive the expected benefit of the medically accepted regimen and therefore the combination could be treated as investigational.

- **Demonstration That Trial Would Not Otherwise Be Conducted**

If a company-sponsor wants to charge for its own investigational drug, or its own approved drug being investigated for a new use, one of the proposed prerequisites is a demonstration by the sponsor that the trial "could not be conducted without charging because the cost of the drug is extraordinary." This proposal is a more demanding standard than the current regulation, which allows charging only if it is necessary to permit the sponsor to conduct the trial but does not require that inability to be the result of the extraordinary cost of the drug itself.

This proposal to reduce the circumstances in which charging may be permitted is inconsistent with a policy of encouraging the conduct of clinical trials, especially trials of off-label uses of approved drugs. FDA has expressed the desirability of manufacturers submitting supplemental applications to obtain FDA approval of off-label uses, but the cost of conducting registrational trials often discourages such trials even if a company "could" afford the research. At least in the case of approved drugs that might be studied for additional uses, FDA should consider allowing charging for the drugs if a company demonstrates that it would not conduct the trial in the absence of permission to charge, not that it could not.

To the extent that a test of financial feasibility is retained, we request that FDA clarify how the standard will be interpreted in the case of a company like J&J, which has numerous operating companies that have their own budgets and conduct their businesses in a decentralized manner. We do not expect FDA to analyze corporate structures, but the rules should establish a fair method of determining financial infeasibility when the sponsor has corporate affiliates with their own separate resources.

- **Drugs Subject to Medicare Coverage with Evidence Development**

The Centers for Medicare & Medicaid Services ("CMS") has adopted a policy under which Medicare may cover a drug being investigated in a clinical trial, even though such a use would not ordinarily be eligible for Medicare coverage.[4] The purpose of the policy, called coverage with evidence development, is to generate research data on new therapies, while at the same time making the therapies available to Medicare beneficiaries in the controlled setting of a clinical trial. In implementing the policy, CMS identifies specific clinical trials in which Medicare will pay for the investigational drugs involved.

The Medicare coverage policy is pointless if FDA rules prohibit charging for drugs in circumstances in which Medicare is willing to reimburse for the drugs in order to develop a body

[4] Guidance for the Public, Industry, and CMS Staff -- National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development (July 12 , 2006), available at http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8.

of research data. FDA should permit sponsors and investigators to charge for drugs subject to Medicare coverage with evidence development.

Amount of Permitted Charge

The Proposed Rule:

When charging for an investigational drug is permitted, the current regulations limit the price to an amount covering the costs of "manufacture, research, development, and handling." The proposal would reduce the permitted charge by limiting the price to an amount covering the "direct" manufacturing, shipping, and handling costs and would expressly exclude consideration of costs primarily incurred to produce the drug in commercial quantities, as well as research, development, administrative, and other costs that would be incurred even if the clinical trial did not occur. In the case of an expanded access program, the price could include recovery of costs associated with administering that program.

If charging is permitted for an approved drug obtained by the study sponsor from another manufacturer, the proposal would limit the price charged to the acquisition cost plus direct costs to ship and handle the drug.

Comments:

- **Charges for Approved Drugs**

Our primary concern with the proposed rules on the amount of the permitted charge is with the proposed limit on the charges for approved drugs. When approved drugs are used in clinical trials, they are typically not furnished by the sponsor, as the proposal appears to contemplate. Rather, physician-administered drugs are usually purchased by the investigator, who bills the patient's health insurance. Other drugs might be furnished by the investigator writing a prescription for the patient, who fills the prescription at a pharmacy that bills the patient's insurance.[5] The proposed regulations do not appear to take these customary distribution methods into account.

The proposal to limit the charge for approved drugs to acquisition plus handling costs, instead of permitting investigators and pharmacies to seek normal reimbursement amounts, would create serious administrative problems. Investigators would need to establish separate billing and inventory accounting systems so that they could identify the cost of a particular drug given to a study subject and adjust the billing accordingly. Different rules would apply to the various drugs in a study since normal reimbursement could apparently be sought for supportive care drugs, while special rules would apply to active controls. Handling costs would somehow have to be estimated and documented in a manner that would sustain scrutiny. The large extra administrative burden in complying with the proposed restrictions could discourage investigators from participating in trials. To the extent that community pharmacies are furnishing drugs used

[5] Occasionally, the appearance of an approved drug used as an active control might need to be altered to resemble the investigational drug to create adequate study blinding. In such a case, the sponsor would provide the approved drug to the investigators to furnish to patients.

in clinical trials, the proposal to limit what they can charge seems infeasible, since they would not even be aware of the customer's status as a clinical trial subject.

When the Medicare program allows reimbursement for drugs used in clinical trials, there are no special restrictions on the amount of the permitted charge. Medicare reimburses for those drugs at its standard payment rates. FDA should not take a more restrictive position than its sister agency on this issue.

We strongly recommend that, when charging for approved drugs is permitted, investigators, pharmacies, and any others involved in their distribution should be allowed to charge their usual amounts for such drugs and to seek normal insurance reimbursement amounts.

- **Effect Under Laws with Price Reporting Obligations**

Although the proposal is not clear, it appears that a manufacturer-sponsor using its own approved drug as an active control, or its own approved drugs in combination with an investigational drug, may be permitted to charge a price for those approved drugs that is limited to recovery of direct manufacturing and handling costs, rather than the price it charges for the same drugs outside of the clinical trial. This has potentially serious consequences under federal laws requiring price reporting and establishing related price or reimbursement controls.

Under the Medicaid Rebate Program[6] and the so-called 340B Program,[7] state Medicaid programs, many private entities receiving grants under the Public Health Service Act, and certain hospitals are entitled to pricing, rebates, and discounts for a drug based in part on the "best price" that a manufacturer offers to any purchaser of that drug during each calendar quarter. It appears that a manufacturer charging clinical trial subjects the small price permitted for a marketed drug under the FDA proposal could be required to include that price in its determination of its "best price," thereby potentially triggering a large liability for rebates and discounts with respect to product purchased for normal medical practice outside the clinical trial. Similarly, such pricing could be construed to establish most favored customer pricing that would be used to set prices under the Federal Supply Schedule contracts with the federal government.[8]

In these cases, FDA's proposal to require a sponsor to charge less than its normal price for a marketed drug could have serious adverse financial effects. This is reason enough to permit usual charges for marketed drugs. In the event that FDA requires reduced charges, FDA should coordinate with other relevant federal agencies to assure that these prices are excluded from setting best price and federal government prices.

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[6] 42 U.S.C. § 1396r-8.

[7] 42 U.S.C. § 256b.

[8] 48 C.F.R. § 552.238-75.

- **Charges for Unapproved Drugs**

Compared to the current regulation, the proposal would significantly lower the price that could be charged for an unapproved drug when charging is permitted. While we understand FDA's concern about certain types of costs, such as commercial plant construction costs, being recouped through the sale of investigational drugs, we question whether the proposed restrictions may go too far.

Especially in the case of expanded access programs, where FDA's objective is making an important drug available to patients who have no comparable or better alternative therapy available, the relatively small costs recoverable under the proposal may make the opportunity to charge irrelevant. Companies will decide whether to offer expanded access based on other factors. This likely consequence seems inconsistent with the purpose of expanded access, and FDA may want to reconsider its stringent limitation on the amount of the permitted charge.

Prior Approval by FDA

The Proposed Rule:

The proposal would require prior written authorization from FDA before a sponsor could charge for an investigational drug. The sponsor would need to show that the criteria for charging are satisfied and would need to justify the amount to be charged.

Comments:

While prior FDA authorization for charging is appropriate for unapproved drugs and the sponsor's own approved drugs being investigated for a new use, it is unnecessary and administratively burdensome in the case of approved drugs.

The proposal would permit charging for approved drugs if the trial is adequately designed and the drug is not available for free. Whether the drug is available for free does not require FDA review, and FDA's review of the trial protocol during the IND process would seem to be fully sufficient to assess whether the trial is adequately designed. It is difficult to imagine circumstances in which FDA would, for IND purposes, allow a trial protocol to be implemented but conclude that charging is impermissible because the trial is not adequately designed. The redundant review under the proposed charging regulations is unnecessary, and charging for approved drugs in the categories specified in the proposal should be permitted without FDA's written authorization in each instance.

Similarly, FDA review of the proposed amount of the charge is unnecessary for approved drugs. If FDA accepts our recommendation to permit normal charges and reimbursement, FDA review would be unnecessary. Even under the terms of the proposal, which would allow acquisition and handling costs to be recovered, FDA would have little to review, since acquisition costs could vary from purchase to purchase in the future and the amount paid would not be within the discretion of the sponsor.

If some sort of agency review is required to allow charging for approved drugs, FDA should adopt a less burdensome approach, such as allowing charging unless FDA objects within thirty days after receiving notice of an intent to charge. A requirement for prior FDA approval could be retained if sponsors are seeking to charge for unapproved drugs or approved drugs being studied for unapproved purposes.

IND-Exempt Trials

The current regulations setting forth the criteria for an exemption from the IND requirements, 21 C.F.R. § 312.2(b), provide that IND-exempt trials must nevertheless comply with the provisions of § 312.7. The prohibition in § 312.7(d) against charging for drugs does not apply to IND-exempt trials, however, because by its terms it is limited to clinical trials "under an IND."

The proposed regulations appear to continue the policy of not imposing charging restrictions on drugs used in IND-exempt trials. Although the text of the proposed regulation no longer limits the prohibition on charging to trials "under an IND," the proposed rules on charging would appear in a new § 312.8, and nothing in the proposal would make compliance with § 312.8 a condition for exemption from the IND requirements.

FDA should explicitly state that the proposed rules on charging in § 312.8 do not apply to IND-exempt trials. The principal bases for an exemption from the IND requirements are that the drugs used in the trial are lawfully marketed and are used in a manner that does not significantly increase the risks to patients, and that the trial is not intended to support labeling or advertising changes. In those circumstances, the use of the drugs is similar to ordinary medical practice, and charging should be permitted in the same manner as in ordinary medical practice.

Technical Conforming Changes and Clarifications

There are provisions in the FDA regulations that should be clarified to take into account the use of approved drugs for non-investigational purposes in clinical trials.

- **Package Labeling**

For example, 21 C.F.R. § 312.6(a) requires that the immediate package of an investigational new drug bear a label advising that the drug is limited by law to investigational use. Since the definition of an investigational new drug is, as described above, potentially very broad, this regulation could be interpreted as requiring active controls and other approved drugs used in trials to bear the (false) statement that the drug use is legally limited to investigational use.

- **Promotion**

Similarly, 21 C.F.R. § 312.7 prohibits promotion of an investigational new drug. The regulation should be clarified to plainly permit an approved drug to be promoted outside of a clinical trial for its approved uses, even if it is used in a clinical trial.

- **Adverse Experience Reporting**

The proposal to regulate charges for other companies' drugs used in clinical trials as active controls or in combination with investigational drugs raises a question about the responsibility of sponsors to report adverse experiences in clinical trials that are associated with approved drugs used for FDA-approved or other medically accepted uses. We request that FDA clarify the sponsor's reporting obligations in such cases.

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Thank you for the opportunity to comment on this proposal.

Sincerely,

Kathy J. Schroeher
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